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Tumor Necrosis Factor Antagonist Therapy and Lymphoma Development

Twenty-Six Cases Reported to the Food and Drug Administration

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Objective. **Etanercept and infliximab are tumor necrosis factor (TNF) antagonists that have been recently approved for the treatment of rheumatoid arthritis (RA) and Crohn's disease (CD). This study was undertaken to investigate the occurrence of lymphoproliferative disorders in patients treated with these agents.**

Methods. **Relevant data in the MedWatch postmarket adverse event surveillance system run by the US Food and Drug Administration were reviewed.**

Results. **We identified 26 cases of lymphoproliferative disorders following treatment with etanercept (18 cases) or infliximab (8 cases). The majority of cases (81%) were non-Hodgkin's lymphomas. The interval between initiation of therapy with etanercept or infliximab and the development of lymphoma was very short (median 8 weeks). In 2 instances (1 infliximab, 1 etanercept), lymphoma regression was observed following discontinuation of anti-TNF treatment, in the absence of specific cytotoxic therapy directed toward the lymphoma.**

Conclusion. **Although data from a case series such as this cannot establish a clear causal relationship between exposure to these medications and the risk of lymphoproliferative disease, the known predisposition of patients with RA and CD to lymphoma, the known excess of lymphoma in other immunosuppressed populations, and the known immunosuppressive effects of the anti-TNF drugs provide a biologic basis for concern and justification for the initiation of additional epidemiologic studies to formally evaluate this possible association.**

In 1998 the Food and Drug Administration (FDA) approved 2 tumor necrosis factor (TNF) antagonists for human use. Etanercept is a dimeric fusion protein of the extracellular ligand binding portion of the human TNF receptor (p75), linked to the Fc portion of a human IgG molecule. It is indicated for the treatment of rheumatoid arthritis (RA) in patients whose disease has not responded to other disease-modifying antirheumatic drugs. Infliximab is a chimeric monoclonal antibody that binds specifically and directly to human TNFα and neutralizes its biologic activity. It is indicated for the treatment of moderate to severely active Crohn's disease (CD) and of RA.

Lymphoproliferative disorders, especially non-Hodgkin's lymphoma, occur at an increased rate in immunodeficient or immunosuppressed patients (1). Patients with RA are also at increased risk of lymphoproliferative disease, both non-Hodgkin's lymphoma and Hodgkin's disease (2–11). Some of this risk appears intrinsic to the natural history of untreated RA and has been attributed to the dysregulated immune function that is part of the pathophysiology of the disease (2–5,7,12). An excess risk of lymphoma has also been reported in patients with CD, although the risk does not

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Table 1. Lymphomas occurring in patients treated with etanercept*

Patient	Age/sex	Lymphoma cell type	Weeks from first etanercept dose to lymphoma diagnosis	Vital status	Immunosuppressive drugs		CTD	EBV associated with lymphoma
					MTX	Other		
1	69/F	Diffuse large B cell NHL	2	Alive	C	–	–	NR
2	84/F	Large cell NHL	8	Alive	C	–	SLE	NR
3	66/F	Diffuse large B cell NHL (recurrent)	4	Dead	–	–	NR	NR
4	45/F	Small T cell NHL	4	Dead	Unknown	CYC	DM	NR
5	67/F	Diffuse large B cell NHL	8	Alive	C	–	–	NR
6	61/F	Diffuse large cell NHL	8	Alive	C	–	–	NR
7	69/F	B cell NHL, n.o.s.	16	Alive	–	AZA	–	NR
8†	48/F	Follicular mixed small and large cell NHL	8	Alive	C	AZA	SS	NR
9	61/M	Mantle cell B cell NHL	8	Alive	C	Unknown	–	NR
10	76/F	NHL, n.o.s.	12	Alive	P	Unknown	NR	NR
11	50/F	NHL, n.o.s.	40	Alive	C	Unknown	NR	NR
12‡	73/M	Mantle cell B cell NHL	3	Alive	P	AZA, INF	NR	NR
13	60/M	B cell NHL	40	Alive	C	–	–	Negative
14	57/M	Large cell NHL	8	Alive	C	–	–	NR
15	75/F	Small lymphocytic B cell NHL	36	Alive	–	–	SS	NR
16	55/M	Diffuse large cell NHL (recurrent)	NR	Dead	–	–	–	NR
17§	44/M	Type B1 thymoma	12	Alive	P	–	–	NR
18	68/M	Hodgkin's disease, nodular sclerosing subtype	52	Alive	P	–	–	NR

* MTX = methotrexate; CTD = connective tissue disease (other than rheumatoid arthritis); EBV = Epstein-Barr virus; NHL = non-Hodgkin's lymphoma; C = concurrent with etanercept; NR = not reported; SLE = systemic lupus erythematosus; CYC = cyclophosphamide; DM = dermatomyositis; n.o.s. = not otherwise specified; AZA = azathioprine; SS = Sjögren's syndrome; P = prior to etanercept; INF = infliximab.
† Father reported to have died of non-Hodgkin's lymphoma at age 53.
‡ Patient received infliximab therapy for 2 years prior to being switched to etanercept. He developed lymphoma 3 weeks after beginning etanercept therapy, and is included in this table because he was taking etanercept at the time lymphoma developed.
§ Patient showed radiographic and histologic evidence of tumor shrinkage after etanercept was discontinued. Traditional antilymphoma chemotherapy was never administered.

appear to be as great as that seen in RA (13,14), and contradictory reports have been published (15). In some studies, the apparent excess of lymphoma in CD patients appears to be, at least in part, independent of exposure to immunosuppressive medications (16).

However, a proportion of the RA- or CD-associated lymphoproliferative disorders has also been attributed to the immunosuppressive effects of the medications used to treat these diseases, most notably azathioprine (AZA), cyclophosphamide, and methotrexate (MTX) for RA (17–22) and AZA for CD (15,23,24). Further support for the hypothesis that medication-related immunosuppression plays an etiologic role in these settings is the clinical observation that a fraction of the lymphomas regress when these treatments are discontinued, without specific antilymphoma chemotherapy having been instituted (25–28).

Another important feature of immunosuppression-associated lymphomas is the relationship between many of these malignancies and infection with the Epstein-Barr virus (EBV), a well-established cause of lymphoma in immunosuppressed patients, particularly in those who have undergone organ transplantation (29,30). Some lymphoproliferative disorders observed in patients with RA have been shown to be associated with EBV (21,28).

In the present report, 26 cases of lymphoproliferative disease in patients receiving etanercept or infliximab therapy are described. The possible relationship between these lymphoproliferative neoplasms and concurrent therapy with TNF antagonists is explored.

METHODS

We examined MedWatch reports submitted to the Food and Drug Administration (FDA) for the biologic products etanercept and infliximab. MedWatch is the FDA's postmarket adverse event surveillance system that receives and tabulates submitted reports of possible medication-related toxicities. All reports citing neoplasms, benign or malignant, were reviewed. Any report with a keyword of lymphoma or that mentioned lymphoma in the text was investigated further. The cases reported to MedWatch through December 2000 comprise the basis for the current summary.

Physicians, nonphysician health care practitioners, or others who submitted these reports were contacted first by phone, to alert them of our investigation. A letter was then sent to the adverse event reporter by both fax and mail,

requesting further information on the reported cancer, including 1) the interval between the initiation of etanercept or infliximab therapy and lymphoma diagnosis; 2) the site of cancer origin; 3) history of a connective tissue disorder other than RA; 4) previous or concurrent exposure to immunosuppressive agents; 5) evidence of lymphoma regression after etanercept or infliximab was stopped, but prior to antilymphoma therapy; 6) results of any laboratory studies performed to assess whether the patient's lymphoma might have been related to EBV infection; and 7) a copy of the lymphoma pathology report. Physicians were also asked to send representative surgical pathology specimens when available. If there was no response to the first letter, a second letter was sent requesting the information.

RESULTS

Etanercept-associated lymphoma. Eighteen cases of lymphoma occurring after the initiation of etanercept therapy were reported to the FDA between May 1999 and December 2000 (Table 1). Three patients were reported to be deceased. Two deaths occurred in patients in whom a previously diagnosed and treated non-Hodgkin's lymphoma recurred after the initiation of etanercept therapy (in both patients the lymphoma was in remission at the time etanercept was begun) and the third occurred in a patient with nodular sclerosing Hodgkin's disease. Lymphoma was diagnosed a median of 8 weeks (range 2–52 weeks) after the initiation of etanercept treatment.

The median age of the patients treated with etanercept was 64 years. The majority of patients were female (61%), and the most common indication for use of etanercept agent was RA (83%) (Table 2). Frequently, patients receiving etanercept were reported to be taking MTX concurrently (9 of 18) or to have a history of prior exposure to MTX (4 of 18), or other immunosuppressive drugs (4 of 18). Sixteen of the etanercept-associated lymphoproliferative disorders were non-Hodgkin's lymphoma, with Hodgkin's disease and thymoma represented by 1 case each. The histologic subtypes of non-Hodgkin's lymphoma in these cases (Table 1), as reported by the original diagnosing pathologist, were generally similar to those previously described in RA patients (7), with diffuse, large B cell lymphoma comprising the largest proportion.

The number of etanercept users in the US through January 2001 is estimated by the manufacturer to be 95,500. A crude approximation of the lymphoma rate among US residents exposed to etanercept would therefore be 18/95,500, or ~19 cases per 100,000 treated persons. This is almost certainly an underestimate, given the known underreporting of adverse events to MedWatch (31).

Table 2. Characteristics of the population of patients who developed lymphoma after treatment with etanercept or infliximab*

Characteristic	Etanercept (n = 18)	Infliximab (n = 8)
Age, years		
25–40	–	2 (25.0)
41–50	4 (22.2)	1 (12.5)
51–60	3 (16.7)	–
61–70	7 (38.9)	3 (37.5)
≥71	4 (22.2)	1 (12.5)
Not specified	–	1 (12.5)
Sex		
Female	11 (61.1)	2 (25.0)
Male	7 (38.9)	5 (62.5)
Not specified	–	1 (12.5)
Indication for TNF antagonist use		
Rheumatoid arthritis	15 (83.3)	3 (37.5)
Psoriatic arthritis	2 (11.1)	–
Crohn's disease	–	5 (62.5)
Not specified	1 (5.6)	–
No. of other medications taken concurrently		
1–3	8 (44.4)	3 (37.5)
4–7	3 (16.7)	3 (37.5)
≥8	4 (22.2)	–
Not specified	3 (16.7)	2 (25.0)
Past or concurrent MTX use	13 (72.2)	2 (25.0)
Past or concurrent use of any immunosuppressive drug (including MTX)	15 (83.3)	4 (50.0)
Weeks from first TNF antagonist dose to lymphoma diagnosis†		
0–8	10 (55.6)	4 (50.0)
9–16	3 (16.7)	–
17–24	–	1 (12.5)
≥25	4 (22.2)	2 (25.0)
Not specified	1 (5.6)	1 (12.5)
Died	3 (16.7)	1 (12)

* Values are the number (%). TNF = tumor necrosis factor; MTX = methotrexate.
† Mean ± SD 15.8 ± 15.6 weeks among etanercept users and 6.2 ± 8.8 weeks among infliximab users.

Infliximab-associated lymphoma. Eight cases of lymphoma occurring after initiation of infliximab treatment were reported to the FDA between May 1999 and December 2000 (Table 3). One patient, with non-Hodgkin's lymphoma, was reported as deceased. These lymphomas occurred a median of 6 weeks (range 2–44 weeks) after the initiation of therapy with infliximab in the 7 cases for which this information was provided.

The median age of the patients with infliximab-associated lymphoma was 62 years. The majority of the infliximab-treated patients were male (62.5%), and the most common treatment indication was CD (62.5%) (Table 2). Other immunosuppressive drugs reported as

Table 3. Lymphomas occurring in patients treated with infliximab*

Patient	Age/sex	Lymphoma cell type	Weeks from first infliximab dose to lymphoma diagnosis	Vital status	Immunosuppressive drugs		CTD	EBV associated with lymphoma
					MTX	Other		
1	77/M	Burkitt's lymphoma	6	Alive	P	–	NR	NR
2	NR	Hodgkin's disease, n.o.s.	NR	Alive	Unknown	Unknown	NR	NR
3	43/F	Hodgkin's disease, nodular sclerosis subtype	44	Alive	–	–	–	NR
4	34/M	Diffuse large B cell NHL	4	Alive	–	6MP	NR	Positive
5†	70/M	Diffuse large cell NHL	6	Alive	–	–	–	NR
6‡	29/M	Hodgkin's disease, nodular sclerosis subtype	2	Alive	–	–	NR	NR
7	68/F	B cell NHL, n.o.s.	24	Alive	C	AZA	–	NR
8	62/M	Large B cell NHL	36	Dead	Unknown	AZA	NR	NR

* Table does not include 1 patient who received infliximab therapy for 2 years prior to being switched to etanercept (patient 12, Table 1). This patient developed lymphoma 3 weeks after beginning etanercept therapy. 6MP = 6-mercaptopurine (see Table 1 for other definitions).
† Patient displayed significant reduction in axillary lymphadenopathy after discontinuation of infliximab, in the absence of standard antilymphoma chemotherapy.
‡ Patient has been reported previously (39).

having been used by these patients included MTX (2 of 8), AZA (2 of 8), and 6-mercaptopurine (1 of 8). Five of the 8 infliximab-associated lymphoproliferative disorders were non-Hodgkin's lymphoma, and 3 were Hodgkin's disease.

The number of infliximab users in the US is estimated by the manufacturer to be ~121,000 as of March 2001. Thus, an estimate of the reported occurrence of lymphoma in infliximab users is 8/121,000, or ~6.6 cases per 100,000 treated persons. As noted above, this estimate is likely to be an underestimate based on underreporting. The uncertainty that underlies the estimates for lymphoma among etanercept users and infliximab users is sufficiently great to prohibit direct comparison of the "rate" of lymphoma associated with the 2 different drugs.

It should be noted that 1 subject in this case series (patient 12 in Table 1) was treated with both agents. He received infliximab for 2 years and then switched to etanercept. Lymphadenopathy was noted after the seventh dose of etanercept. He is tabulated formally among the etanercept users since that was the agent he was taking when the lymphoma developed.

Additional information reported. Additional information was provided in response to our letter, for 11 of 18 etanercept cases (61%) and 5 of 8 infliximab cases (62.5%). Information on EBV status was received for only 2 subjects: 1 etanercept-treated patient was reported as EBV negative, and 1 infliximab-treated patient was reported to be EBV positive.

In 1 case (patient 17 in Table 1), a thymoma was observed to shrink and necrose after the discontinuation of etanercept. In a second patient (patient 5 in Table 3), a significant reduction in axillary lymphadenopathy was reported after discontinuation of infliximab. Both "responses" occurred in the absence of standard antilymphoma chemotherapy. No other information was received from physicians regarding whether attempts were made routinely or systematically to determine if these lymphoproliferative disorders regressed after anti-TNF therapy was discontinued.

Among the patients treated with etanercept for refractory RA, 2 were reported to have had Sjögren's syndrome, and 1 each had dermatomyositis and systemic lupus erythematosus. None of the patients treated with infliximab had a reported history of a connective tissue disease besides RA. The father of 1 etanercept-treated patient was reported to have had non-Hodgkin's lymphoma. In none of the remaining 25 cases was a significant family history of cancer or lymphoproliferative neoplasia reported, although in most instances, information on family history of malignancy was simply not included.

Slides or pathology samples were available from 1 etanercept-treated and 2 infliximab-treated patients. In all 3 cases, the pathologic diagnosis rendered by the referring pathologist was confirmed by review in the National Cancer Institute's Laboratory of Pathology. The lack of pathology specimens from 23 of the 26 patients precluded a more systematic analysis of those data.

DISCUSSION

The FDA's passive postmarket adverse event reporting system (MedWatch) received 18 reports of lymphoma subsequent to the initiation of etanercept therapy and 8 reports of lymphoma subsequent to the initiation of infliximab therapy during the 2½ years since these novel biologic agents were licensed for clinical use in the US. One patient had been exposed to both medications. An estimate of the reporting rate for lymphoma after etanercept therapy, based on the manufacturer's estimates of the number of patients using this drug, is 19/100,000. The reporting rate for lymphoma in infliximab-treated patients is 6.6/100,000. Incomplete ascertainment of cases, and the lack of accurate information regarding the size of the populations exposed to these 2 medications, prevented our calculating reliable lymphoma rates. Thus, we could not determine whether the occurrence of lymphoma in these subjects was greater than that which would have been expected based on general population incidence rates or among untreated patients with RA or CD. The age-adjusted incidence of lymphoma in the US from 1992 to 1998 was 18.3/100,000 (15.7/100,000 for non-Hodgkin's lymphoma and 2.6/100,000 for Hodgkin's lymphoma) (32,33).

Currently available data do not permit us to draw definitive conclusions regarding whether these TNF antagonists were the proximate cause of the reported lymphomas, whether these neoplasms developed as part of the natural history of the underlying medical conditions, or whether they occurred as a complication related to other immunosuppressive medications to which these patients were exposed. Disentangling the relative contributions of innate lymphoma susceptibility, other immunosuppressive medications, and the anti-TNF agents to the development of lymphomas is impossible with the present data. A further complication is the suggestion that lymphoma represents a complication that is specific to the subset of RA patients who have severe disease (12). Clearly, patients who are currently prescribed etanercept or infliximab are those whose RA has proven refractory to standard therapy. Thus, it is conceivable that the apparent lymphoma cluster observed in this setting reflects the selection of a subpopulation of RA patients with particularly aggressive disease, rather than being related to the treatment received by such patients.

TNF is a proinflammatory cytokine that has been implicated in the etiology of both RA (34,35) and CD (36). The activities of TNF are pleiotropic and its role in the immune response incompletely understood. It is biologically plausible that TNF antagonists, which are novel immunomodulatory agents, might produce significant adverse effects, including an increased risk of malignancy. It was recently reported that active tuberculosis and other serious infections were observed soon after the initiation of treatment with infliximab, suggesting immunomodulation as a potential contributor to risk of infection or reactivation of the disease (37).

Both RA and CD are recognized as diseases that are linked to an altered or dysfunctional immune response. Consequently, the issue of increased risk for lymphoproliferative disease has been of interest in both disorders (2,7,13,14). Furthermore, because both RA and CD are treated with immunosuppressive medications, the role of concomitant or prior immunosuppressive therapy has added a layer of complexity in the effort to clarify the causal pathway by which these malignancies arise (17).

There are numerous case series reports of the occurrence of lymphomas, especially non-Hodgkin's lymphomas, in RA patients treated with the folic acid analog MTX (5,18–21). The role of EBV infection in these patients is also of interest (7,20,21,28). In considering whether MTX played an etiologic role in RA-associated lymphoma, Georgescu and Paget (28) noted that the strongest evidence came from well-documented cases in which the lymphoma regressed after the withdrawal of MTX treatment (22). The fact that a majority of the RA patients in the present series had either prior or concurrent exposure to MTX raises the possibility that the anti-TNF agents might further compromise immune function in patients with latent EBV infection, thereby facilitating the evolution of a lymphoproliferative disorder. We cannot discern from available data whether this might have occurred in the absence of MTX exposure.

An excess of lymphomas in patients with CD has also been noted in some studies (13,14), but not all (15). As in RA, it has been suggested that the lymphoma excess in CD is, at least partially, independent of the immunosuppressive therapy used in the disorder (16). AZA is the most commonly prescribed immunosuppressive therapy for CD, and this agent has been implicated in the pathogenesis of lymphoma (17,24). Only 3 patients in this series are known to have been exposed to AZA or its metabolite, 6-mercaptopurine.

In general, the lymphomas that occur in the setting of impaired immune function are B cell, non-Hodgkin's lymphomas, most often large cell lymphomas (3,29), and the same is true in the current series, in which 21 of 26 cases were non-Hodgkin's lymphoma. We believe, however, that it is appropriate to include the

Table 4. Published studies of lymphoma development after etanercept or infliximab treatment*

Authors, year (ref.)	Agent	Diagnosis	No. exposed/no. developing lymphoma†	No. not exposed/no. developing lymphoma
Targan et al, 1997 (40)	Infliximab	CD	102/0	6/0
Rutgeerts et al, 1999 (36)	Infliximab	CD	73/1	NA
Sandborn and Hanauer, 1999 (41)	Infliximab	CD	Part of 394/1‡	ND
Sandborn and Hanauer, 1999 (41)	Infliximab	RA	Part of 394/2‡	ND
Maini et al, 1999 (42)§	Infliximab	RA	340/1¶	88/0
Markham and Lamb, 2000 (35)	Infliximab	RA	771/1	
Bathon et al, 2000 (43)	Etanercept	RA	415/1	217/0
Lovell et al, 2000 (44)	Etanercept	JRA#	69/0	26/0

* Of the 1,993 patients reported from these various series, 7 developed malignant lymphoma. In none of these reports was the risk of lymphoma considered excessive by the authors, but these conclusions are limited by the small number of subjects in each series. Manufacturers have informed us that the report by Rutgeerts et al and the one by Sandborn and Hanauer were on the same lymphoma patient, and that the report by Maini et al and the one by Markham and Lamb were on the same patient. The report by Targan et al was the initial report of the same study subsequently reported by Rutgeerts et al. In the initial protocol, patients received short-term therapy. The later publication described patients from the initial cohort who had responded to therapy and were re-treated for an extended period of time. This table does not represent a count of cases, and there may be other duplications in reporting. NA = not applicable; ND = not determined.

† The lymphoma was Hodgkin's disease in the patient reported by Maini et al and subsequently by Markham and Lamb (see above), and non-Hodgkin's lymphoma in all of the others.

‡ The total patient group included 394 patients, but it was not specified how many of the 394 had Crohn's disease (CD) and how many had rheumatoid arthritis (RA).

§ Lipsky et al published an update of this series in 2000 (45). No additional cases of lymphoma developed during the extended followup.

¶ Maini et al cite the occurrence of 3 additional lymphomas (2 non-Hodgkin's lymphoma, 1 Hodgkin's disease) among 555 patients treated in 6 prior clinical trials, but they do not provide references to these specific studies.

Because this was a study of patients with juvenile rheumatoid arthritis (JRA), the patients were much younger than those in other reported series.

Hodgkin's disease cases in this analysis. This specific lymphoma may well occur at an excess rate in RA (8–11) and in CD (14).

One noteworthy clinical feature of the lymphomas observed in this series is the very short interval ("latent period") between the initiation of anti-TNF therapy and the development of malignancy. Although there likely is a bias toward reporting of events that occur soon after the initiation of new medical treatment, the similarity between the latent period observed in our case series and that which characterizes lymphomas that develop post–organ transplantation is striking. In the latter setting as well, there is a very short interval between initiation of immunosuppressive therapy and development of lymphoproliferative neoplasia.

The majority of posttransplant lymphomas appear to be related etiologically to EBV (29,30). In a fraction of RA-associated lymphomas (7), and perhaps the majority of MTX-related lymphomas (28), there is molecular evidence of EBV infection. This led us to inquire about the EBV status of the lymphoma patients in the current study. We were unable to retrieve sufficient clinical or laboratory data to address this issue. This is a question that should be considered in future studies, because the management of EBV-related lymphoma differs from that of spontaneous lymphoma. Patients with the former are more likely to benefit from a clinical trial of medication withdrawal and observation, in hopes that a "spontaneous remission" will occur (38), thereby sparing a subset of patients the need for cytotoxic chemotherapy.

Recognizing that immunosuppressive medications have increased the risk of certain malignancies in the past, this complication was monitored during the phase II and phase III development of the anti-TNF agents. There have been occasional case reports of lymphoma in patients receiving infliximab for CD (39). These cases were reported to the FDA and are included in our series as infliximab cases 6 and 8 (Table 3). In addition, the development of lymphoproliferative malignancy has been reported in a number of the early trials conducted to establish the efficacy of these agents (Table 4); in each of these trials, the investigators concluded that there was no significant excess of lymphoma. These analyses were, however, based on very small numbers of cases, and thus the reported point estimates of risk (which have very wide confidence intervals) may not accurately reflect the true risk.

We have described 26 cases, reported to the FDA's passive surveillance system, of lymphoma in patients receiving TNF antagonist therapy. A case series such as this cannot establish a cause-and-effect relationship between drugs, such as etanercept and infliximab, and an adverse outcome, such as lymphoma. However, associations identified in this manner may prompt caution in the clinical use of a particular medication and

may provide a rationale for the development of formal epidemiologic studies to assess the purported relationship in a more quantitative manner. The known predisposition of patients with RA and CD to lymphoma, the known excess of lymphoma in other immunosuppressed populations, and the known immunosuppressive effects of the anti-TNF drugs provide a biologic basis for concern, and ample justification for the development of additional studies to formally evaluate this possible association.

Given the nature of the case ascertainment mechanism used in this study, it is unlikely that we have identified all pertinent events (31). The purposes of this report are 1) to bring to the attention of clinicians who prescribe these important new medications the possibility that they *may* be associated with an increased risk of lymphoma; 2) to stimulate heightened awareness of this possible complication of therapy in order to facilitate early diagnosis and treatment (including a trial of withdrawal of anti-TNF prior to institution of chemotherapy, when clinically practical); 3) to encourage the reporting of additional cases, with more clinical detail that might shed new light on our observations; and 4) to encourage the design of methodologically sound epidemiologic studies to test this new hypothesis.

Finally, there are two specific management options which might be considered based on the current case series. Two individuals with previously treated lymphoma that was in remission at the time anti-TNF therapy was initiated very quickly developed recurrent disease and died of fulminant lymphoma. Consideration should be given to classifying such persons as ineligible for treatment with etanercept or infliximab, until the possible relationship of these agents to lymphoma risk has been clarified. Second, if lymphoma develops in a patient receiving anti-TNF therapy, consideration can be given to treating this complication by withdrawing the medication and monitoring the patient for evidence of lymphoma regression, prior to initiating cytotoxic chemotherapy, if the patient's clinical condition permits.

Addendum. Since the completion of this investigation and writing of the manuscript, additional reports of patients receiving anti-TNF medications have continued to accrue within the MedWatch database. That database was searched for additional cases covering the period November 2001 through September 2002. Seventy-five candidate reports of possible lymphomas related to the administration of anti-TNF medications were identified and reviewed. Seven of the cases were not lymphomas. Of the remaining 68 cases, 54 were classified as "probable" medication-associated lymphomas (29 infliximab, 25 etanercept), and 14 were classified as "possible" medication-associated lymphomas (10 infliximab, 4 etanercept).

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